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**Titel des Beitrags:** Histological, immunohistological and molecular characteristics of intraductal precursor of carcinoma ex pleomorphic adenoma support a multistep carcinogenic process.

**Abstract:** In recent years, multistep carcinogenesis of carcinoma ex pleomorphic adenoma (CEPA) has been identified, starting with intraductal neoplasia within pre-existent pleomorphic adenoma (PA). However, as yet there is no consensus regarding clinical relevance and appropriate terminology of precursor lesions in CEPA. We therefore decided to investigate precursor lesions, especially intraductal carcinoma, in a series of 85 cases of CEPA. Intraductal carcinoma confined by benign myoepithelial cells was found in 60 cases and mostly exhibited high-grade cellular atypia, increased cellular proliferation and frequent genetic alterations (TP53, Her2-neu, androgen receptor). Intraductal carcinoma was absent only in the myoepithelial type of CEPA. In 26 cases, purely intraductal CEPA with extensive intraductal expansion was found. This suggests that there is a long period of intraductal growth before extraductal intracapsular infiltration of the PA. We identified two different histomorphological types of intraductal carcinoma, which we call 'clinging' and 'solid' types. In summary, combined histological, immunohistological and molecular data strongly support multistep carcinogenesis starting with intraductal carcinoma for all non-myoepithelial types of CEPA. The clinical significance of our finding of
two histomorphological types of intraductal carcinoma (clinging and solid) is not yet clear. Intraductal carcinoma, intracapsular invasive CEPA and minor extracapsular invasive CEPA (up to about 6 mm) all show favourable prognosis and together comprise half of the cases in our study.